REMARKS

Reconsideration and allowance are respectfully requested.

Claims 34-45 are pending.

The amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

Entry of the amendments is requested to address the Examiner's new objections and rejections. They could not be earlier presented because they were initially raised in Paper No. 14 after the claims had been amended. The amended claims are directed to an expression vector in which a drug-resistance gene has or is linked to an mRNA-destabilizing sequence. Amendment of the claims would reduce the issues on appeal.

Claim Objections

Claims 34-36 were objected to by the Examiner. Applicants traverse and request withdrawal of the objection because the grammar has been corrected.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 34-39 were rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because this rejection in moot in view of the claim amendments.

Claim 39 was rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because a representative number of species within the claimed genus is known in the art as evidenced by citation of *Molecular Cloning* on page 21 of the specification.

The Office Action alleges on page 4 that only prepackaging cells are described for use in the invention. Although pages 19-20 of the specification describe such cells, this allegation is incorrect for the specification as a whole. DNA construction (A) as described on page 8-12 of the specification does not require an LTR and a packaging signal of a retrovirus genome, in contrast to DNA construction (B). The former DNA construction can be used as an expression vector in any type of cell where high-level expression of gene products is to be selected.

But to advance prosecution in this case, claims 40 and 45 have been added in response to this rejection. Therefore, even if the Examiner's allegations are accepted as correct, the specification as originally filed provides a written description of these claims.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 34-39 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The phrase "highly express" has been deleted from claim 35 because this limitation is not required for patentability. Instead, it is now recited that the presence of an mRNA-destabilizing sequence causes higher transcription of the drug-resistance gene under selection with the drug than in the absence of the mRNA-destabilizing sequence.

Similarly the phrase "highly expressing" has been deleted from claim 39 because this limitation is not required for patentability.

Amendment of claims 34-35 moots the Examiner's last rejection. His suggestion is gratefully acknowledged.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that supplies the impetus to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Claims 34-39 were rejected under Section 103(a) as allegedly being unpatentable over Pavlakis et al. (U.S. Patent 5,972,596) in view of the Pharmacia Biotech catalog (1995). Applicants traverse because the cited references fail to teach or suggest the combination of an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence. Therefore, Pavlakis et al. and the Pharmacia Biotech catalog do not render obvious the claimed invention because they do not disclose all limitations of the claims.

Claims 34-38 were rejected under Section 103(a) as allegedly being unpatentable over Pavlakis et al. (U.S. Patent 5,972,596) in view of DePonti-Zilli et al. (Proc. Natl. Acad. Sci. USA 85:1389-1393, 1988). Applicants traverse because, although it was alleged on page 11 of the Office Action that Pavlakis et al. have suggested that the neomycin resistance gene would be an effective reporter in their system, actually this suggestion is absent from the disclosure of the '596 patent. To determine whether putative regulatory sequences are sufficient to confer mRNA stability control, DNA with a suspected inhibitory/instability sequence (INS) is fused to an indicator or reporter gene to create a gene which is transcribed as a hybrid RNA. Col. 13, lines 13-17, of the '596 patent. Neomycin is listed as an example of the indicator or reporter gene. Col. 13, lines 19-21, of the '506 patent. But no expression vector with a functional drug-resistance genes is disclosed by Pavlakis et al. and there is no motivation given in the '596 patent for substituting neomycin as the indicator or reporter in the expression vectors disclosed by Pavlakis et al. It was also admitted in the Office Action that DePonti-Zilli et al. do not teach that the ß-actin gene-*neo* mRNA levels were controlled primarily by transcriptional processes and not by changes in mRNA stability (i.e., they did not teach that their expression vector has an mRNA-destabilizing sequence).

It appears that the Examiner is proposing on page 12 of the Office Action that the combination of these references would have been motivated "to characterize the ability of a putative transcriptional regulatory sequence to affect the stability/utilization of a neomycin resistance gene transcript." This is an inadequate basis for a case of prima facie obviousness. Pavlakis et al. list several different indicator or reporter genes, including a neomycin resistance gene. There is no suggestion in either reference for

selecting the neomycin resistance gene over any of the other listed indicator or reporter gene if the objective is merely to characterize a suspected INS. Certainly DePonti-Zilli et al. were not successful in showing that an mRNA-destabilizing sequence could be characterized using such expression vectors. Furthermore, it was neither taught nor suggested by the cited references that an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence could be used to select for high-level expression in drug-resistant cells as the claimed invention is able to do.

Therefore, it is submitted that no evidence has been presented in the Office Action that one of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner because there is no teaching or suggestion for using a neomycin resistance gene instead of any other indicator or reporter gene to characterize a suspected INS.

Claims 34-38 were rejected under Section 103(a) as allegedly being unpatentable over Pavlakis et al. (U.S. Patent 5,972,596) in view of Gritz et al. (Gene 25:179-188, 1983). Applicants traverse for reasons similar to those stated above.

Pavlakis et al. does not teach an expression vector with a drug-resistance gene. Like DePonti-Zilli et al., Gritz et al. teach a drug-selectable expression vector with a drug-resistance gene (hygromycin) but it is not used to characterize a suspected INS.

It appears that the Examiner is proposing on page 15 of the Office Action that the combination of these references would have been motivated "to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by direct genetic selection, as taught by Gritz et al." This is an inadequate basis for a case of prima facie obviousness. Pavlakis et al. list several different indicator or reporter genes, but it does not appear that there is any description of a hygromycin resistance gene. Nor is there any suggestion in either reference for selecting the hygromycin resistance gene over any of the other listed indicator or reporter gene if the objective is merely to characterize a suspected INS. Certainly Gritz et al. were not concerned with characterizing an mRNA-destabilizing sequence. Furthermore, it was neither taught nor suggested by the cited references that an expression vector with a drug-resistance gene having or linked to an mRNA-

destabilizing sequence could be used to select for high-level expression in drug-resistant cells as the claimed invention is able to do.

Therefore, it is submitted that no evidence has been presented in the Office Action that one of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner because there is no teaching or suggestion for using a hygromycin resistance gene instead of any other indicator or reporter gene to characterize a suspected INS.

Claims 34-38 were rejected under Section 103(a) as allegedly being unpatentable over Pavlakis (U.S. Patent 5,972,596) in view of de la Luna et al. (Gene 62:121-126 1988). Applicants traverse.

Pavlakis et al. does not teach an expression vector with a drug-resistance gene. Like DePonti-Zilli et al., de la Luna et al. teach a drug-selectable expression vector with a drug-resistance gene (puromycin) but it is not used to characterize a suspected INS.

It appears that the Examiner is proposing on page 17 of the Office Action that the combination of these references would have been motivated "to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by genetic selection, as taught by de la Luna et al." This is an inadequate basis for a case of prima facie obviousness. Pavlakis et al. list several different indicator or reporter genes, but it does not appear that there is any description of a puromycin resistance gene. Nor is there any suggestion in either reference for selecting the puromycin resistance gene over any of the other listed indicator or reporter gene if the objective is merely to characterize a suspected INS. Certainly de la Luna et al. were not concerned with characterizing an mRNA-destabilizing sequence. Furthermore, it was neither taught nor suggested by the cited references that an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence could be used to select for high-level expression in drug-resistant cells as the claimed invention is able to do.

Therefore, it is submitted that no evidence has been presented in the Office Action that one of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner because there is no teaching or suggestion for

using a puromycin resistance gene instead of any other indicator or reporter gene to characterize a suspected INS.

Withdrawal of the Section 103 rejection is requested because the invention as claimed would not have been obvious to a person of ordinary skill in the art at the time it was made.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claims 34-36 and 38-39 were rejected under Section 102(b) as allegedly being anticipated by Treisman (Cell 42:889-902, 1985). Applicants traverse because the cited reference fails to teach or suggest an expression vector with a drug-resistance gene having or linked to an mRNA-destabilizing sequence. Therefore, Treisman does not anticipate the claimed invention because it does not disclose all limitations of the claims.

Withdrawal of the Section 102 rejection is requested.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 14), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

The claims are amended as follows.

34. (Amended) An expression vector comprising a selectable drug-resistance gene having [, as a selection marker, and] an mRNA-destablizing sequence, which produces a short-lived transcript of the drug-resistance gene.

35. (Amended) An expression vector comprising a drug-resistance gene linked to [, as a selection marker, and] an mRNA-destablizing sequence, wherein said expression vector confers drug resistance when transfected into a cell and the drug-resistance gene is transcribed at a higher rate under selection with the drug because of the presence of the mRNA-destabilizing sequence [is a vector for producing cells which highly express gene products encoded by said vector, through transfecting cells with said vector and selecting the cells with said drug].

36. (Amended) The expression vector as set forth in claim 35, in which the mRNA-destablizing sequence is an mRNA-destabilizing sequence of [non-translated sequence of] a c-fos gene.

38. (Amended) Cells into which the expression vector as set forth in claim 35 has been transferred and selected with the drug.

39. (Amended) A process for producing cells [highly] expressing a gene product[s] encoded by the expression vector as set forth in claim 35, comprising:

(a) transferring the expression vector into [the] cells,

(b) selecting cells which express the drug resistance gene from the transferred expression vector, and

(c) expressing the gene product encoded by the expression vector in the selected cells.

Claims 40-45 are added as new claims.